UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/662,462	09/15/00	SMITH T	2551-49

HM22/0910

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EXAMINER	
GOLDBERG, J	
ART UNIT	**PAPER NUMBER**
1655	15

DATE MAILED: 09/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/662,462	Applicant(s) SMITH ET AL.	
	Examiner Jeanine A Enewold Goldberg	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed August 10, 2001. Currently, claims 12-18, 24-40 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn.

3. This action contains new grounds of rejection.

4. Claims 24-40 have been examined on the merits.

DETAILED ACTION

Priority

5. This application claims priority to a PCT document, a provisional and an EP document. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Response to Arguments

The response has failed to insert the first line of the specification claiming priority to the provisional application.

The examiner acknowledges the receipt of the priority document EP 99870109.8.

Sequence Rules

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

While applicants have added SEQ ID NO: to the claims, the specification fails to identify all of these sequences by SEQ ID NO:. For example, page 37 of the specification, lines 13-14.

Claim Objections

7. Claims 28, 30, 32, 34 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Specifically, Claims 28, 30, 32, 34 depend on Claim 27 which is directed to methods using SEQ ID NO: 1-13 only. Claims 28, 30, 32, 34 are directed to methods which use these probes as well as SEQ ID NO: 33-38. Thus, the claims are not further limiting.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 38, 40 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A1) Claim 38 is indefinite because Claim 38 depends on Claim 37. Claim 37 is directed to oligonucleotides which are specific for Candida. Thus, it is unclear how Claim 38 is intended to limit the claims with respect to the Aspergillus, Cryptococcus and Pneumocystis pathogens. The SEQ ID NO:s in Claim 37 do not correspond to these organisms as provided in the specification.

B1) Claim 40 is indefinite over the recitation "the oligonucleotide probes comprise a homopolymer tail which is added at the 3' or 5' extremity of the probe". Claim 40 depends on Claim 24. Claim 24 appears to be using specific probes which are limited to the sequences of SEQ ID NO: 1-13, 33-38 not to sequences comprising these SEQ ID NO:s. Thus, it is unclear whether Claim 40 is intended to further limit these claims or whether the claims are not further limiting. It is unclear whether the SEQ ID NO:s already comprise the homopolymer tail or whether the oligonucleotides are intended to further comprise these tails. Thus, the metes and bounds of the claims are unclear.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 37-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Williams et al. (J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28).

The claims have been amended be limited to oligonucleotides having SEQ ID NO: 2-13 or 33-38. Having is considered open claim language.

Williams teaches the ITS region of C. albicans, C. tropicalis and C. krusei. SEQ ID NO: 1, **2, 3, 6, 9, 33, 36** are embedded within the ITS region (limitations of Claims 37 and 38). Thus, Williams teaches oligonucleotides having SEQ ID NO: 2, 3, 6, 9, 33, 36.

10. Claims 37-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Botelho et al (Yeast, Vol. 10, pages709-717, 1994).

The claims have been amended be limited to oligonucleotides having SEQ ID NO: 2-13 or 33-38. Having is con0sidered open claim language.

Botelho teaches the ITS1 and ITS2 regions of C. albicans, and C. tropicalis. SEQ ID NO: 1, **2, 3, 6, 33, 36** are embedded within the ITS region (limitations of Claims 37 and 38). Thus, Botelho teaches oligonucleotides having SEQ ID NO: 2, 3, 6, 33, 36.

11. Claims 37-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al. (Genbank Accession Number U10987, March 1996) or Lin et al (J. of Clincial Microbiology, Vol. 33, No. 7, pages 1815-1821, July 1995).

The claims have been amended be limited to oligonucleotides having SEQ ID NO: 2-13 or 33-38. Having is considered open claim language.

Lin et al (herein referred to as Lin) teaches the ITS1 and ITS2 of Candida parapsilosis. SEQ ID NO: **4** and **5** are embedded within the ITS region (limitations of Claims 37 and 38). Thus, Lin teaches oligonucleotides having SEQ ID NO: 4 and 5.

12. Claims 37-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Messner et al. (Genbank Accession Number U09325, May 1994).

The claims have been amended be limited to oligonucleotides having SEQ ID NO: 2-13 or 33-38. Having is considered open claim language.

Messner et al (herein referred to as Messner) teaches the ITS1 and ITS2 of Kluyveromyces. SEQ ID NO: **7** and **8** are embedded within the ITS region (limitations of Claims 37 and 38). Thus, Williams teaches oligonucleotides having SEQ ID NO: 7, 8.

13. Claims 37-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Williams et al. (Genbank Accession Number L47108, September 1995).

The claims have been amended be limited to oligonucleotides having SEQ ID NO: 2-13 or 33-38. Having is considered open claim language.

Williams et al (herein referred to as Williams) teaches the ITS1 of Candida glabrata. SEQ ID NO: **10** is embedded within the ITS region (limitations of Claims 37 and 38). Thus, Williams teaches oligonucleotides having SEQ ID NO: 10.

14. Claims 37-38 are rejected under 35 U.S.C. 102(e) as being anticipated by Lott et al. (US Pat. 6,242,178, June 5, 2001).

The claims have been amended be limited to oligonucleotides having SEQ ID NO: 2-13 or 33-38. Having is considered open claim language.

Lott et al (herein referred to as Lott) teaches the ITS2 of Candida dubliniensis. SEQ ID NO: **11** and **12** are embedded within the ITS region (limitations of Claims 37 and 38). Thus, Lott teaches oligonucleotides having SEQ ID NO: 11 and 12.

15. Claims 37-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Lott et al. (Genbank Accession Number U96719, August 1997).

The claims have been amended be limited to oligonucleotides having SEQ ID NO: 2-13 or 33-38. Having is considered open claim language.

Lott et al (herein referred to as Lott) teaches the ITS2 of Candida dubliniensis. SEQ ID NO: **11** and **12** are embedded within the ITS region (limitations of Claims 37 and 38). Thus, Lott teaches oligonucleotides having SEQ ID NO: 11 and 12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Newly Added Claims 24-28, 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Botelho et al. (Yeast, Vol. 10, pg. 709-717, 1994) in view of Hogan (US Pat. 5,595,874, January 1997).

Botelho et al (herein referred to as Botelho) teaches specific identification of *Candida albicans* by hybridization with oligonucleotides derived from ribosomal DNA internal spacers. Botelho teaches an alignment of *Candida albicans* and *Candida tropicalis*. Botelho teaches that the ITS1 and ITS2 regions were found to contain distinct regions with sufficient sequence divergence to make them suitable as specific target sites for the identification of *C. albicans*. Botelho teaches that comparison of the ITS sequences was performed by computer-aided sequence comparison using the software SEQNCE and FASTA to find optimal sequence alignment. SEQ ID NO: 1, 2, 3, 6, 36 are embedded within the ITS1 region (limitations of Claim 37-38). The sequences are found in regions of variability. Botelho teaches detecting and identifying fungal pathogenic species in a sample by releasing the nucleic acids of the pathogens, amplifying the ITS with a fungal universal primer pair, hybridizing the nucleic acids with a species specific oligonucleotide probe, and detecting the complexes formed (pg. 714-715). Botelho teaches that the probes which were identified unequivocally distinguish between *C. albicans* and other yeast generas as well as between .*C albicans* and other medically important Candida strains such that the have great potential as diagnostic tools (pg. 715, col.

2). Botelho teaches that the ITS1 and ITS2 regions have low interspecies homology which makes them ideal probes to differentiate species.

Botelho does not specifically teaches the exact probes and primers of the instant application.

However, Hogan et al. (herein referred to as Hogan) teaches variable regions can be identified by comparative analysis of sequences by using a Sun Microsystem ™ computer for comparative analysis. The "compiler is capable of manipulating many sequences of data at the same time. Computers of this type and computer programs which may be used or adapted for the purposes are commercially available" (col. 5, lines 50-60). Hogan also teaches the use of specific primers col. 6-7, lines 50-67, lines 1-12, and furthermore provides specific guidance for the selection of primers and probes.

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10^{o}C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have designed probes and primers to Candida, as taught by Botehlo, to the regions of variability found between the two species such that the two species may be differentiated as taught by Hogan. The skilled artisan would have been motivated to have designed probes and primers to these Candida species for the benefit of differentiating the

species from one another. Botelho teaches that the probes which were identified unequivocally distinguish between *C. albicans* and other yeast generas as well as between .*C albicans* and other medically important Candida strains such that the have great potential as diagnostic tools. Thus, the ordinary artisan would have been specifically motivated to identify and differentiate the Candida species. The knowledge in that art at the time the invention was made was extremely high for aligning sequences and finding regions of variability such that sequence comparison and differentiation between internal spacer regions to identify regions of either variability or conservation was well known and studied. The art teaches an alignment of known sequences, namely *Candida albicans,* and *Candida tropicalis,* as taught by Botelho. Identifying regions of variability between the two species to generate probes which are species specific is as taught by Hogan. Within the alignment provided between a select group of the Candida species provided by Botelho, the instant probes are within regions of variability. The ordinary artisan would have been motivated to have designed probes and primers to the region of variability of the ITS1 region to detect either *C. albicans* or *C. tropicals*. Thus, in view of the teachings in the art, a method for detecting fungal pathogenic species using the probes of SEQ ID NO: 1-3, 6, 33, 36 are obvious.

Response to Arguments

The response traverses the rejection.

The response asserts that the designing of probes that are able to differentiate the 7 Candida species was not at all straightforward. This argument has been reviewed but is not convincing because the claims are not drawn to differentiating the 7 Candida species. The claims are merely directed to detecting one of the fungal pathogens or detecting a specific species.

The response asserts that not all Candida ITS sequences were known at the time of the instant invention. This argument has been reviewed but is not convincing because each of the Candida species claimed was known prior to June 11, 1998.

The response asserts that the "inventors experienced a great amount of cross-reactivity of the probes with unknown ITS sequence from other Candida species and from other fungal species present in the patient's sample". This argument has been reviewed but is not convincing because arguments of counsel are not found to be persuasive in the absence of a factual showing. MPEP 716.01(c) makes clear that

> "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

Thus, applicant's assertions that there was cross-reactivity must be supported by an appropriate affidavit or declaration.

The response asserts that the probes of the present invention are designed to specifically function in the hybridization assay of the present invention. Applicant's asserts that the tailing of the probe affects the efficiency of the assay. This argument has been reviewed but is not convincing because the claims are drawn broadly to a generic hybridization assay and product claims. Claim 40 directed to homopolymer tails on the probes is the only claim which appears as though it may be directed to the unexpected results. However, as provided above, attorney statements are not evidence and must be supported by an appropriate affidavit or declaration include statements regarding unexpected results. The instant Table is not provided in the appropriate form with the unexpected results explained. For example, is unclear what the

3' or 5' tailing comprises. Further, the claims are not commensurate in scope with the unexpected results.

Thus for the reasons above and those already of record, the rejection is maintained.

17. Newly Added Claims 24-28, 30, 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) in view of Hogan (US Pat. 5,595,874, January 1997).

Williams et al (herein referred to as Williams) teaches an alignment of *Candida albicans*, *Candida tropicalis* and *Candida krusei*. Williams teaches obtaining sequences and retrieving sequences from GenBank and EMBL for alignment using CLUSTAL V suite of programs. SEQ ID NO: 1, 2, 3, 6, 9, 33, 36 are embedded within the ITS1 region (limitations of Claims 37 and 38). The sequences are found in regions of variability. Williams teaches ITS1 and ITS4 and ITS1 and ITS2 as primers used to amplify DNA extracted from Candida isolates and archival tissue (limitations of Claim 26). Moreover Williams teaches the Genbank Accession Numbers for six of the Candida species (L47111, L47112, L47114, L47109, L47113, L47107 and L47108). These Genbank Accession Numbers contain SEQ ID NO: 1-10, 33-37. Williams specifically teaches that "the ability to identify Candida within human tissue provides an opportunity to increase our knowledge of the role of candidal species in disease. This is particularly important for patients with CHC because of the association between this form of candidiasis and the development of oral cancer" (pg. M27).

Williams does not specifically teaches the exact probes and primers of the instant application.

However, Hogan et al. (herein referred to as Hogan) teaches variable regions can be identified by comparative analysis of sequences by using a Sun Microsystem ™ computer for

comparative analysis. The "compiler is capable of manipulating many sequences of data at the same time. Computers of this type and computer programs which may be used or adapted for the purposes are commercially available" (col. 5, lines 50-60). Hogan also teaches the use of specific primers col. 6-7, lines 50-67, lines 1-12, and furthermore provides specific guidance for the selection of primers and probes.

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> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10^{o}C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have designed probes and primers to Candida, as taught by Williams, to the regions of variability found between the two species such that the two species may be differentiated as taught by Hogan. The skilled artisan would have been motivated to have designed probes and primers to detect and/or differentiate these Candida species for the benefit of differentiating the species from one another. Williams specifically teaches that "the ability to identify Candida within human tissue provides an opportunity to increase our knowledge of the role of candidal species in disease. This is particularly important for patients with CHC because of the association between this form of candidiasis and the development of oral cancer" (pg. M27). Thus, the ordinary artisan would have been specifically motivated to identify and differentiate the Candida species. The knowledge in that art at the time the

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Response to Arguments

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The response asserts that not all Candida ITS sequences were known at the time of the instant invention. This argument has been reviewed but is not convincing because each of the ITS1 regions and ITS2 regions claimed were known prior to June 11, 1998.

The response asserts that many other ITS sequences from other fungal species, were not known. This argument has been reviewed but is not convincing because the instant invention has not identified all fungal species which may be present in a patient's sample and determined their sequence.

The response asserts that the "inventors experienced a great amount of cross-reactivity of the probes with unknown ITS sequence from other Candida species and from other fungal species present in the patient's sample". This argument has been reviewed but is not convincing because arguments of counsel are not found to be persuasive in the absence of a factual showing. MPEP 716.01(c) makes clear that

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Thus for the reasons above and those already of record, the rejection is maintained.

18. Newly Added Claims 24-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Lin (Genbank Accession Number U10987, March 1996) or Lin et al (J. of Clincial Microbiology, Vol. 33, No. 7, pages 1815-1821, July 1995) or Messner et al (Genbank Accession Number U09325, May 1994) or Williams et al (Genbank Accession Number L47108, September 1995) in view of Hogan (US Pat. 5,595,874, January 1997).

Williams et al (herein referred to as Williams) teaches an alignment of *Candida albicans*, *Candida tropicalis* and *Candida krusei*. Williams teaches obtaining sequences and retrieving sequences from GenBank and EMBL for alignment using CLUSTAL V suite of programs. SEQ ID NO: 1, 2, 3, 6, 9, 33, 36 are embedded within the ITS1 region (limitations of Claims 37 and 38). The sequences are found in regions of variability. Williams teaches ITS1 and ITS4 and ITS1 and ITS2 as primers used to amplify DNA extracted from Candida isolates and archival tissue (limitations of Claim 26). Moreover Williams teaches the Genbank Accession Numbers for six of the Candida species (L47111, L47112, L47114, L47109, L47113, L47107 and L47108). These Genbank Accession Numbers contain SEQ ID NO: 1-10, 33-37. Williams specifically teaches that "the ability to identify Candida within human tissue provides an opportunity to increase our knowledge of the role of candidal species in disease. This is particularly important for patients with CHC because of the association between this form of candidiasis and the development of oral cancer" (pg. M27).

Lin et al (herein referred to as Lin) teaches the ITS1 region of Candida parapsilosis which comprises SEQ ID NO: 4 and SEQ ID NO: 5.

Messner et al (herein referred to as Messner) teaches the ITS1 region of Kluyveromyces marxianus which comprises SEQ ID NO: 7 and 8 (anamorph Candida kefyr).

Williams et al (herein referred to as Williams) teaches the ITS1 of Candida glabrata which comprises SEQ ID NO: 10.

Neither Williams-1, Linn, Messner nor Williams-2 specifically teaches the exact probes and primers of the instant application.

However, Hogan et al. (herein referred to as Hogan) teaches variable regions can be identified by comparative analysis of sequences by using a Sun Microsystem ™ computer for comparative analysis. The "compiler is capable of manipulating many sequences of data at the same time. Computers of this type and computer programs which may be used or adapted for the purposes are commercially available" (col. 5, lines 50-60). Hogan also teaches the use of specific primers col. 6-7, lines 50-67, lines 1-12, and furthermore provides specific guidance for the selection of primers and probes.

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> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10^{o}C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have designed probes and primers to Candida, as taught by Williams-1, Linn, Messner or Williams-2, to the regions of variability found between the two species such that the two species may be differentiated as taught by Hogan. The skilled artisan would have been motivated to have designed probes and primers to detect and/or differentiate

these Candida species for the benefit of differentiating the species from one another. Williams specifically teaches that "the ability to identify Candida within human tissue provides an opportunity to increase our knowledge of the role of candidal species in disease. This is particularly important for patients with CHC because of the association between this form of candidiasis and the development of oral cancer" (pg. M27). Thus, the ordinary artisan would have been specifically motivated to identify and differentiate the Candida species. The knowledge in that art at the time the invention was made was extremely high for aligning sequences and finding regions of variability such that sequence comparison and differentiation between internal spacer regions to identify regions of either variability or conservation was well known and studied. The art teaches an alignment of known sequences, namely *Candida albicans, Candida tropicalis, Candida krusei*, as taught by Williams. Aligning additional sequences known in the art at the time of the invention would have been routine as provided in Williams and Hogan. Identifying regions of variability between the species to generate probes which are species specific is taught by Hogan. Thus, in view of the teachings in the art, a method for detecting fungal pathogenic species using the probes of SEQ ID NO: 4-5, 7-8, 10 are obvious.

19. Newly added Claims 24, 27, 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lott et al (US Pat. 6,242,178, June 2001) in view of Hogan (US Pat. 5,595,874, January 1997).

Lott et al (herein referred to as Lott) teaches numerous ITS2 regions from Candida organisms. Lott teaches that the nuclei acid molecules described are useful as probes to detect, identify and distinguish or differentiate between Candida species in a sample or specimen with high sensitivity and specificity. Lott continues to state that "it will be understood

that the probes provided herein are merely exemplary and that those skilled in the art could identify additional portions or fragments of each ITS2 sequence to be used as species-selective probes without undue experimentation from the sequences provided" (col. 5, lines 40-45). Furthermore, the ITS2 region for each Candida species offers a number of very unusual sequences for use as PCR primers. Therefore, comparisons can be made between the Candida ITS2 sequence of two or more species to identify unique or non-homologous regions that would be useful to construct probes that would be specific for distinguishing between those Candida and have minimal cross-hybridization with ITS21 regions from other species. (col. 5, lines 50-60). The specification also provides a computer program for generating selective probes. Lott teaches the ITS2 region of Candida dubliniensis. Probes and primers which are species specific were identified. SEQ ID NO: 12 taught by Lott is the ITS2 region of C. dubliniensis. Namely, SEQ ID NO: 35 overlaps 15 of the nucleotides from the instant SEQ ID NO: 12.

Neither Lott et al or Lott specifically teaches the exact probes and primers of the instant application.

However, Hogan et al. (herein referred to as Hogan) teaches variable regions can be identified by comparative analysis of sequences by using a Sun Microsystem ™ computer for comparative analysis. The "compiler is capable of manipulating many sequences of data at the same time. Computers of this type and computer programs which may be used or adapted for the purposes are commercially available" (col. 5, lines 50-60). Hogan also teaches the use of specific primers col. 6-7, lines 50-67, lines 1-12, and furthermore provides specific guidance for the selection of primers and probes.

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is

recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10^{o}C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have designed probes and primers to Candida, as taught by Lott et al, to the regions of variability found between the two species such that the two species may be differentiated as taught by Hogan. The skilled artisan would have been motivated to have designed probes and primers to differentiate these Candida species for the benefit of differentiating the species from one another. The ordinary artisan would have been specifically motivated to identify and differentiate the Candida species within the ITS2 region. The knowledge in that art at the time the invention was made was extremely high for aligning sequences and finding regions of variability such that sequence comparison and differentiation between internal spacer regions to identify regions of either variability or conservation was well known and studied. There is a reasonable expectation of success for aligning known sequences, as taught by Lott et al with the *Candida dubliniensis* sequence of Lott using known computer alignment methods and identifying regions of variability between the species to generate probes which are species specific, as taught by Hogan. Within the alignment provided between a select group of the Candida species provided by Lott, the instant probes

are within regions of variability. Thus, in view of the teachings in the art, a method for detecting fungal pathogenic species using the probes of SEQ ID NO: 11-12 are obvious.

20. Claims 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Botelho et al. (Yeast, Vol. 10, pg. 709-717, 1994) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to Claims 24-28, 30 above further in view of Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, pg. 962-967, April 1995).

21. Claims 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to Claims 24-28, 30, 32 above further in view of Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, pg. 962-967, April 1995).

22. Claims 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Lin (Genbank Accession Number U10987, March 1996) or Lin et al (J. of Clincial Microbiology, Vol. 33, No. 7, pages 1815-1821, July 1995) or Messner et al (Genbank Accession Number U09325, May 1994) or Williams et al (Genbank Accession Number L47108, September 1995) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to claims 24-28, 30, 32 above, and further in view of Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, pg. 962-967, April 1995).

23. Claims 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lott et al (US Pat. 6,242,178, June 2001) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to Claims 24, 27, 34 above, and further in view of Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, pg. 962-967, April 1995).

Neither Williams, Botelho, Lin, Messner, Lott, nor Hogan specifically teach detection of fungal species using a solid support.

However, Fujita et al (herein referred to as Fujita) teaches the detection of Candida species in blood using the ITS2 region of the species. Fujita specifically teaches a microtitration plate hybridization assay where digoxigenin- and biotin labeled oligonucleotide probes were detected in an EIA by capture with streptavidin-coated microtitration plates. The microtitration plates were coated with a single-stranded DNA for hybridization studies. As seen in Table 2, a matrix format against DNA from other Candida species as well as from other fungi was used. All probes were tested against all of the target DNAS so that the pattern of reactivity could be detected (pg. 964). Fujita teaches that PCR products were previously detected with Southern blotting or EtBr staining of agarose gels, but these methods are less sensitive that the microtitration plate EIA. Specifically Fujita teaches that microtitration plate EIA detection of C. albicans DNA following PCR is easier and more rapid than that by Souther blotting (pg. 966, col. 1).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified methods of Williams, Botelho, Linn, Messner or Williams-2 or Lott in view of Hogan with the teachings of Fujita. The ordinary artisan would have readily recognized the improvements of solid support detection as taught by Fujita for the detection of PCR amplified DNA. The ordinary artisan would have been motivated to have detected the PCR amplified DNA using a microtitration plate EIA for the express benefits of increased sensitivity, ease and speed, as described by Fujita. Thus, the ordinary artisan would have detected the fungal pathogens using probes from variable regions of the Candida species, as taught by Williams and Botelho or Lott et al in view of Hogan, on a solid support at taught by Fujita.

Response to Arguments

The response traverses the rejection. The response asserts that the examiner has combined six references. In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991). Further, the examiner would like to point out that six references have not been combined. The statement of rejection contains an "or" which combines the two rejections above for the convenience of saving space.

The response also asserts that as argued above the probes and primer were not obvious. However, as stated above, the probes and primers are obvious absent unexpected results or other secondary considerations. The response argues that Fujita and Jordan teach hybridization assay on a solid support, but they lack the teaching of how to select probes that function as 3' or 5' tailed probes in the hybridization assay of the invention. The limitations of adding a homopolymer tail is only provided in New Claim 40.

Thus for the reasons above and those already of record, the rejection is maintained.

24. Claims 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Botelho et al. (Yeast, Vol. 10, pg. 709-717, 1994) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to Claims 24-28, 30 above further in view of Jordan (US Pat. 6,017,699, January 2000).

25. Claims 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to Claims 24-28, 30, 32 above further in view of Jordan (US Pat. 6,017,699, January 2000).

26. Claims 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Lin (Genbank Accession Number U10987, March 1996) or Lin et al (J. of Clincial Microbiology, Vol. 33, No. 7, pages 1815-1821, July 1995) or Messner et al (Genbank Accession Number U09325, May 1994) or Williams et al (Genbank Accession Number L47108, September 1995) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to claims 24-28, 30, 32 above, and further in view of Jordan (US Pat. 6,017,699, January 2000).

27. Claims 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lott et al (US Pat. 6.242.178, June 2001) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to Claims 24, 27, 34 above, and further in view of Jordan (US Pat. 6,017,699, January 2000).

Neither Williams, Botelho, Lin, Messner, Lott, nor Hogan specifically teach detection of fungal species using a solid support.

However, Jordan teaches five species-specific primers and probes for Candida. Jordan teaches that a multiplex PCR amplification and agarose gel electrophoretic detection (Figure 4). Jordan teaches, in Example IV, three approaches of carrying out detection and/or confirmation of the four species of Candida (col. 16). Within these approaches, Jordan teaches coating a 96 well plate with biotin labeled primer for detection. Jordan also teaches that "use of the PCR master mix containing all 3 newly designated species-specific primer pairs resulted in accurate amplification of the predicted sized fragment for the DNA template added" (col. 21, lines 9-20). The multiplex approach to DNA amplification was successful. Jordan teaches significant increase in the level of sensitivity for detecting the candidal organism (Table 4)" (col. 19).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified methods of Williams and Botelho or Lott in view

of Hogan with the teachings of Jordan. The ordinary artisan would have readily recognized the improvements of solid support detection as taught by Jordan for the detection of PCR amplified DNA simultaneously. The ordinary artisan would have been motivated to have detected the PCR amplified DNA which has a "significant increase in the level of sensitivity for detecting the candidal organism (Table 4)". Thus, the ordinary artisan would have detected the fungal pathogens using probes from variable regions of the Candida species, as taught by Williams and Botelho or Lott in view of Hogan, on a solid support at taught by Jordan.

Response to Arguments

The response traverses the rejection. The response asserts that the examiner has combined six references. In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991). Further, the examiner would like to point out that six references have not been combined. The statement of rejection contains an "or" which combines the two rejections above for the convenience of saving space.

The response also asserts that as argued above the probes and primer were not obvious. However, as stated above, the probes and primers are obvious absent unexpected results or other secondary considerations. The response argues that Fujita and Jordan teach hybridization assay on a solid support, but they lack the teaching of how to select probes that function as 3' or 5' tailed probes in the hybridization assay of the invention. The limitations of adding a homopolymer tail is only provided in New Claim 40.

28. New Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Claims 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Botelho et al. (Yeast, Vol.

10, pg. 709-717, 1994) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to Claims 24-28, 30 above further in view of Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, page 962-967, April 1995) and Tomblike et al (US Pat. 4,617,102, October 1986).

29. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to Claims 24-28, 30, 32 above further in view of Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, page 962-967, April 1995) and Tomblike et al (US Pat. 4,617,102, October 1986).

30. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Lin (Genbank Accession Number U10987, March 1996) or Lin et al (J. of Clincial Microbiology, Vol. 33, No. 7, pages 1815-1821, July 1995) or Messner et al (Genbank Accession Number U09325, May 1994) or Williams et al (Genbank Accession Number L47108, September 1995) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to claims 24-28, 30, 32 above, and further in view of Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, page 962-967, April 1995) and Tomblike et al (US Pat. 4,617,102, October 1986).

31. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lott et al (US Pat. 6,242,178, June 2001) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to Claims 24, 27, 34 above, and further in view of Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, page 962-967, April 1995) and Tomblike et al (US Pat. 4,617,102, October 1986).

32. Neither Williams nor Botelho nor Linn nor Messner nor Williams-2 nor Lott nor Hogan specifically teach isolating fungal pathogens from blood.

However, Fujita et al (herein referred to as Fujita) teaches the detection of Candida species in blood using the ITS2 region of the species. Fujita specifically teaches unlike urine or

sputum, blood is a normally sterile fluid (pg. 965, col. 2). Fujita teaches that Candida sp. DNA from blood, particularly from that of persistently granulocytopenic patients, raises the suspicion of deep-seated infection. Moreover, Fujita teaches that a PCR-based test for candidemia should be more sensitive than conventional blood culture methods since DNA from dead blastoconidia, as well as that from viable blastoconidia, is detected and the target sequence is amplified many fold. Fujita teaches lysing erthrocytes and leukocytes by adding 0.8 ml of TE buffer (10mM tris, 1 mM EDTA, pH 8.0) (pg. 963, col. 1).

Tomblike et al (herein referred to as Tomblike) teaches a blood lysis procedure which consists of adding 0.5 ml of whole blood with 4.0 ml of DNA lysis buffer, such buffer consisting of 10mM tris-HCL, pH 7.4, 10 mM NaCl, 10 mM EDTA and mixing.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified teachings of Williams and Botelho or Lott in view of Hogan to further extract the fungal pathogens from blood as taught by Fujita under conditions of Tomblike. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the conditions selected was other than routine as compared to the closest prior art. The ordinary artisan would have been motivated to have sampled blood from a patient to determine the candida status of the blood. Fujita specifically teaches that blood is blood is sterile and amenable to sensitive detection. Further the ordinary artisan would have modified the lysis procedure to obtain optimal results.

Response to Arguments

The response traverses the rejection.

The response also asserts that as argued above the probes and primer were not obvious. However, as stated above, the probes and primers are obvious absent unexpected results or other secondary considerations. The response argues that Fujita and Jordan teach hybridization assay on a solid support, but they lack the teaching of how to select probes that function as 3' or 5' tailed probes in the hybridization assay of the invention. The limitations of adding a homopolymer tail is only provided in New Claim 40.

33. Newly added Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Botelho et al. (Yeast, Vol. 10, pg. 709-717, 1994) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to Claims 24-28, 30 above further in view of Shah et al (US Pat. 5,558,989, September 1996).

34. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to Claims 24-28, 30, 32 above further in view of Shah et al (US Pat. 5,558,989, September 1996).

35. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Lin (Genbank Accession Number U10987, March 1996) or Lin et al (J. of Clincial Microbiology, Vol. 33, No. 7, pages 1815-1821, July 1995) or Messner et al (Genbank Accession Number U09325, May 1994) or Williams et al (Genbank Accession Number L47108, September 1995) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to claims 24-28, 30, 32 above, and further in view of Shah et al (US Pat. 5,558,989, September 1996).

36. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lott et al (US Pat. 6,242,178, June 2001) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to

Claims 24, 27, 34 above, and further in view of Shah et al (US Pat. 5,558,989, September 1996).

Neither Williams, Botelho, Lin, Messner, Lott, nor Hogan specifically teach using homopolymer tail on the oligonucleotides for purpose of detection.

However, Shah teaches that tailed capture probes serve two purpose such that they are complementary to DNA and they link the hybridization complex to a solid support making it possible to separate the hybridization complex from the remainder of the sample (col. 3, lines 30-37). Shah teaches that the capture probes are characterized generally by a homopolymer.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified methods of Williams, Botelho, Linn, Messner, Williams-2 or Lott in view of Hogan with the teachings of Shah. The ordinary artisan would have readily recognized the improvements of solid support detection using a homopolymer tail as taught by Shah for the detection of PCR amplified DNA simultaneously. The ordinary artisan would have been motivated to have detected the probes using tails for the express benefit of separating the hybridization complex from the remainder of the sample. Thus, the ordinary artisan would have detected the fungal pathogens using probes from variable regions of the Candida species, as taught by Williams and Botelho or Lott in view of Hogan, on a solid support with homopolymer tails as taught by Shah.

Conclusion

37. No claims allowable over the art.

38. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
September 6, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600